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(54) Multiparticulate sustained release medicament

(57) A multiparticulate sustained release drug delivery system, e.g. comprising small tablets contained in a gelatin or other rapidly dissolving capsule, comprises particles containing (a) an ionically charged bioactive ingredient or a salt or ester thereof (b) a release-sustaining and binding medium which is a polymer having an anhydroglucose backbone and (c) an ionic substance having a charge opposite to component (a) or a salt or ester thereof. Component (b) is preferably a hydroxyalkyl alkylcellulose ether or methylcellulose ether and component (c) may be finely divided particles of cross-linked ion exchange resin.

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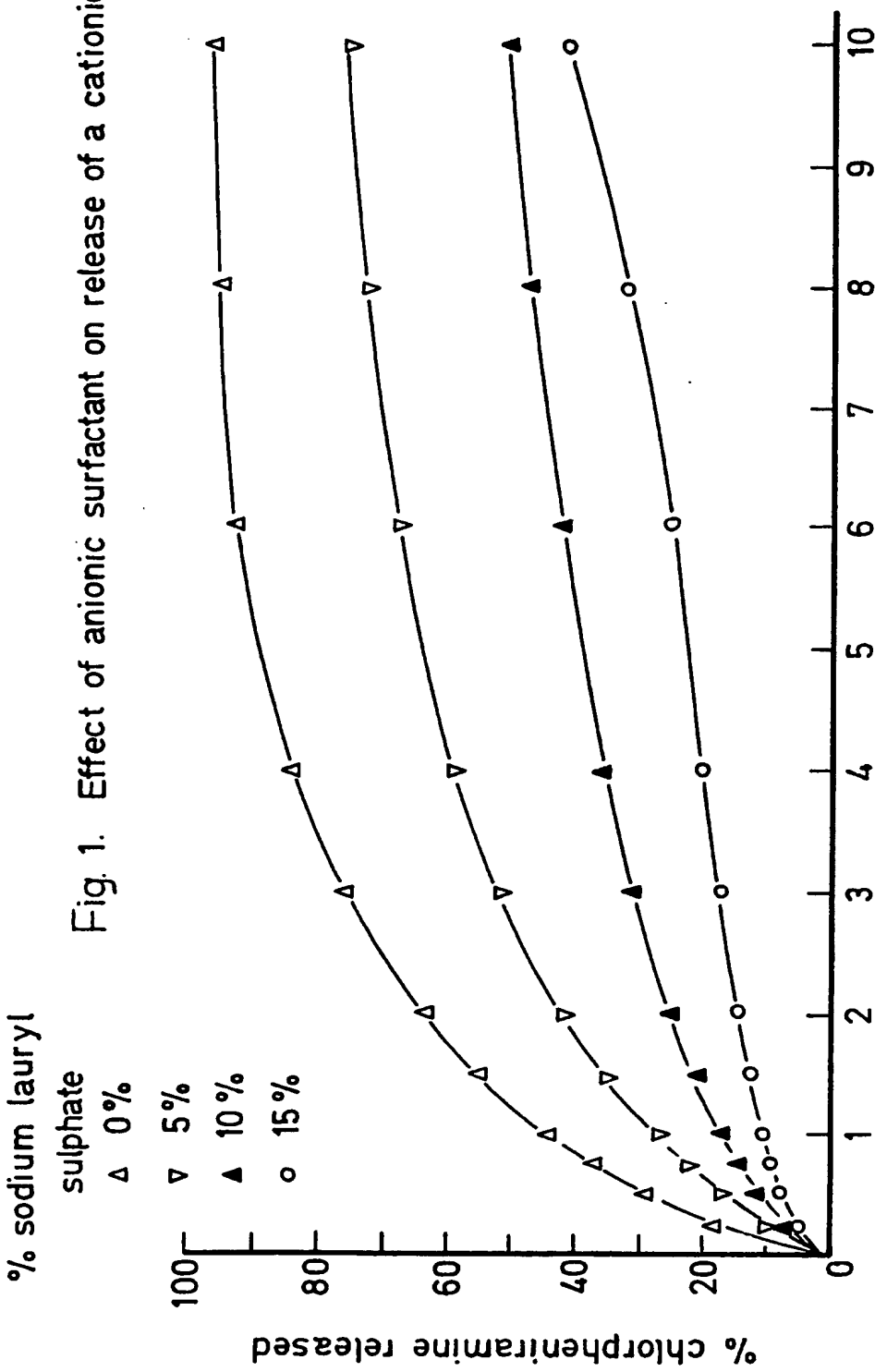


Fig. 1. Effect of anionic surfactant on release of a cationic drug.

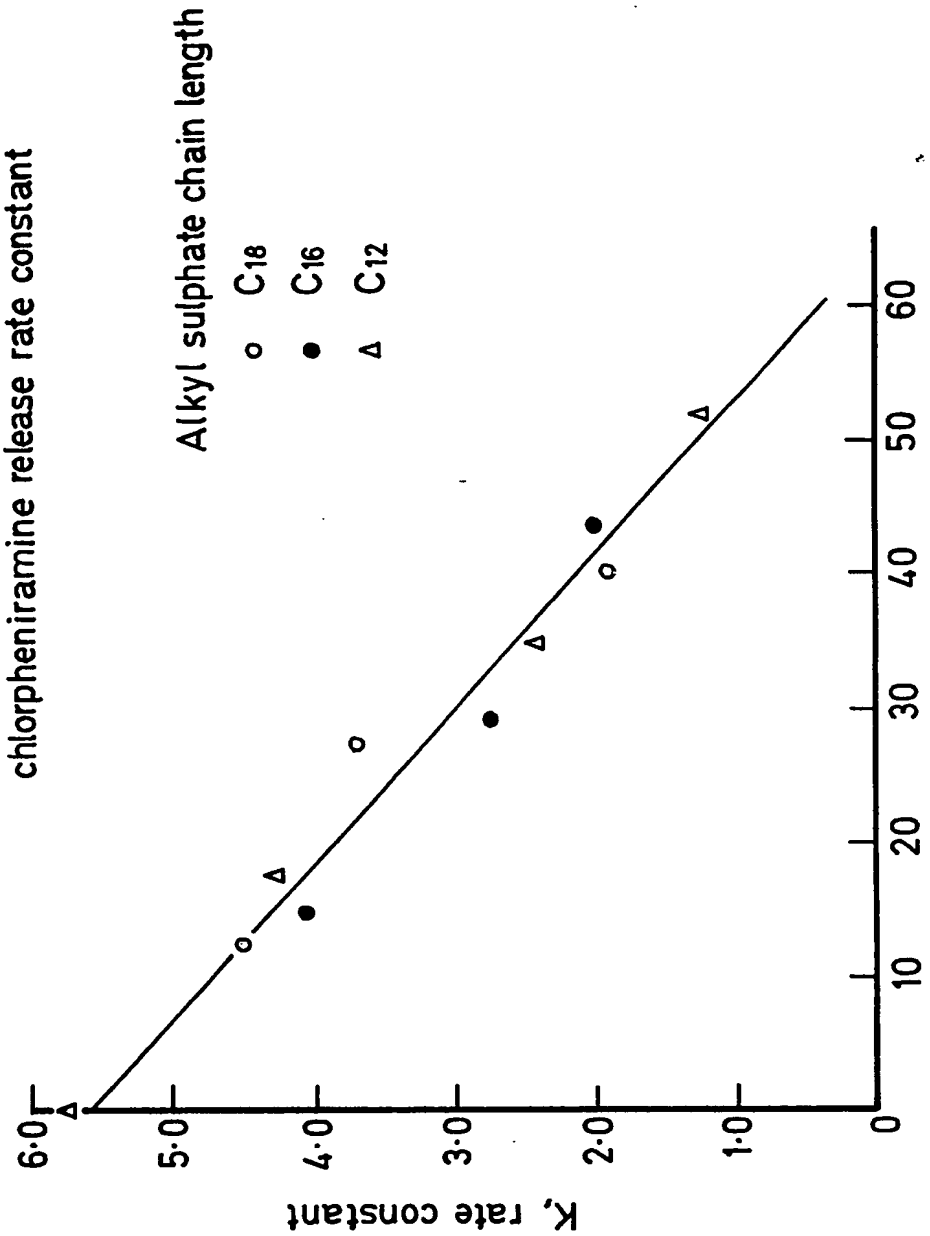


Fig.2. Effect of alkyl sulphate concentration on chlorpheniramine release rate constant

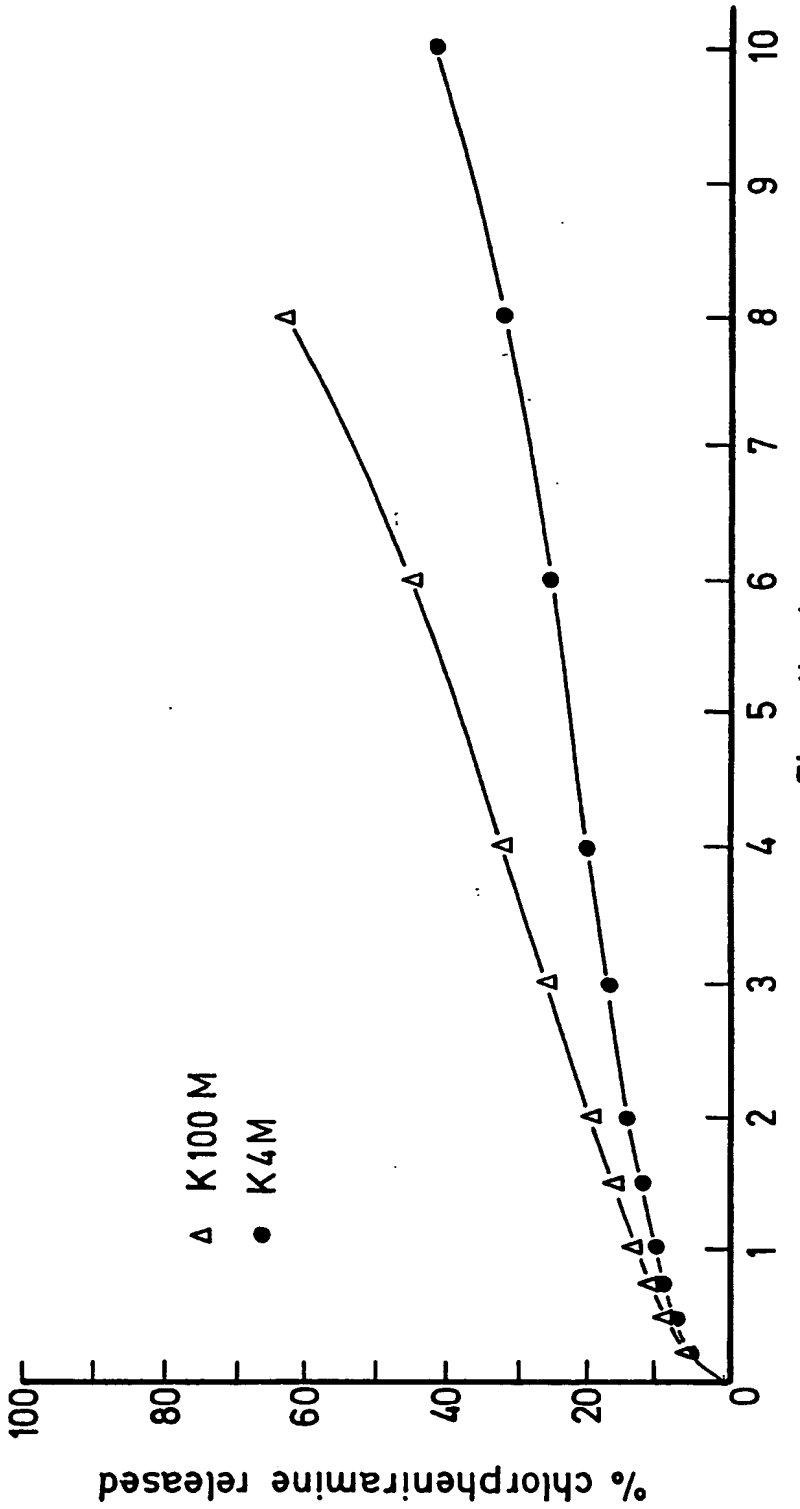
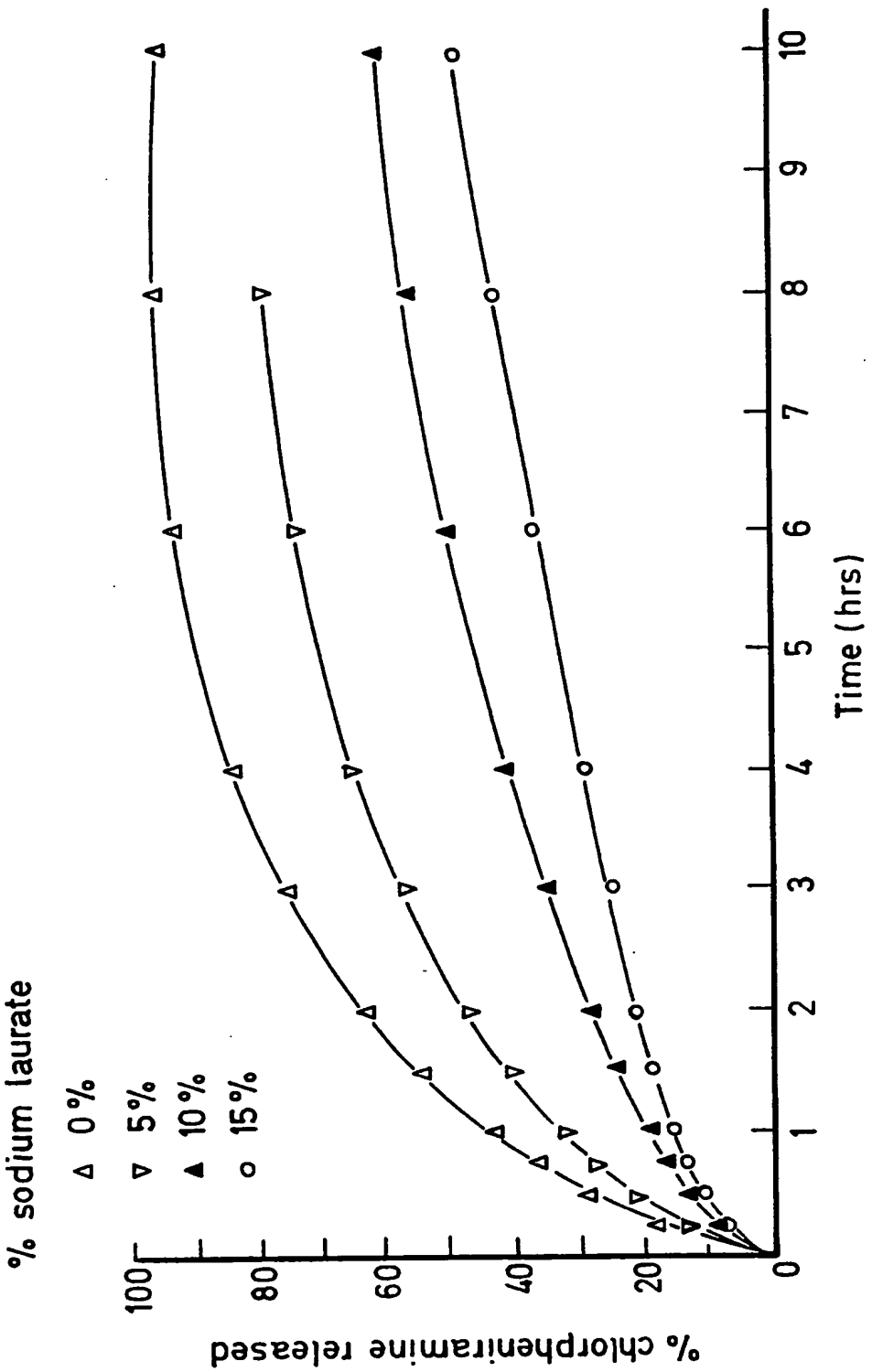


Fig. 3. Effect of sodium lauryl sulphate (15%) on chlorpheniramine release from HPMC, — K100M and K4M matrices.

Fig. 4. Effect of sodium carboxylate on cationic drug release



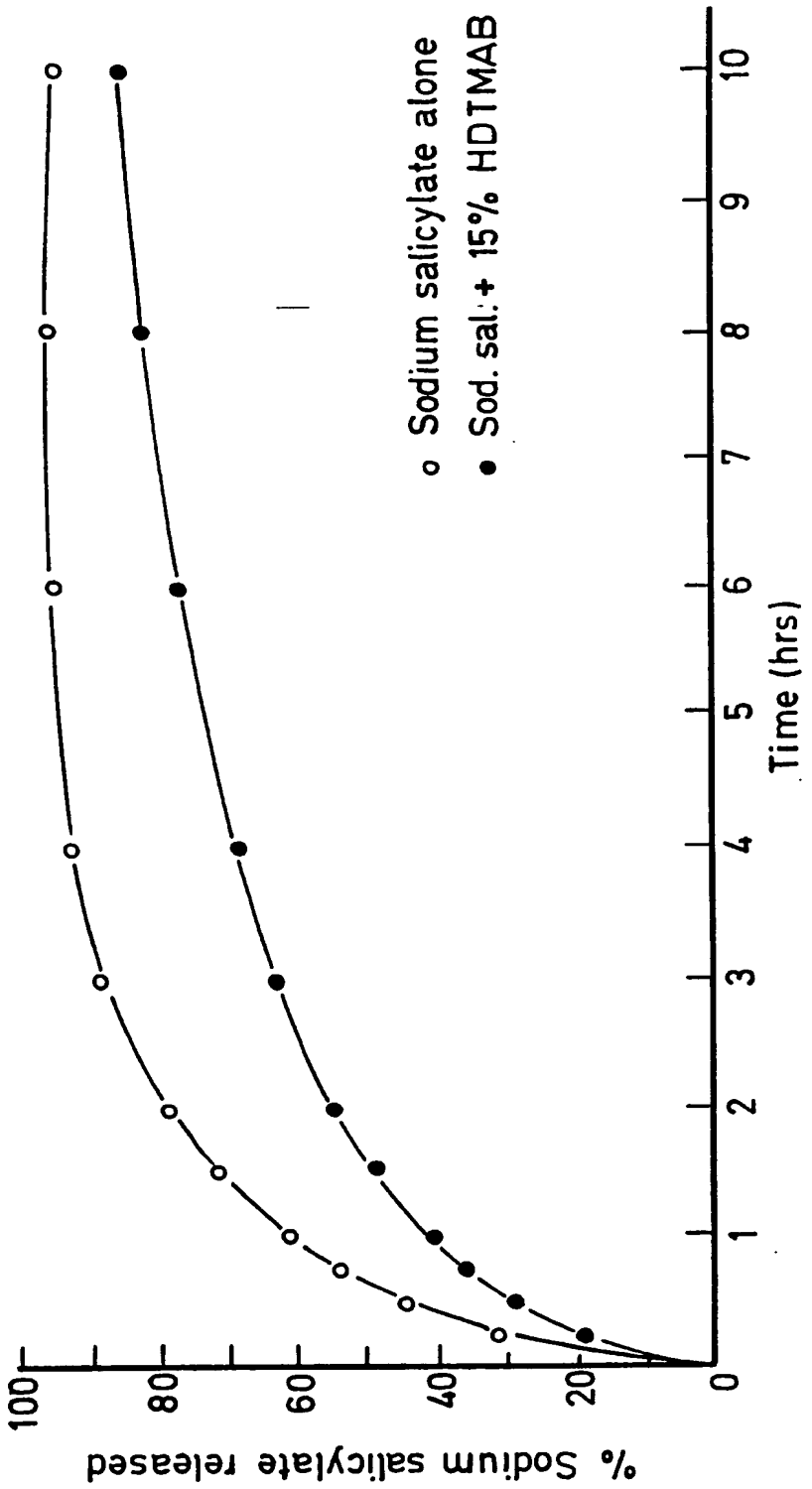


Fig. 5. Effect of cationic surfactant on release of an anionic drug.

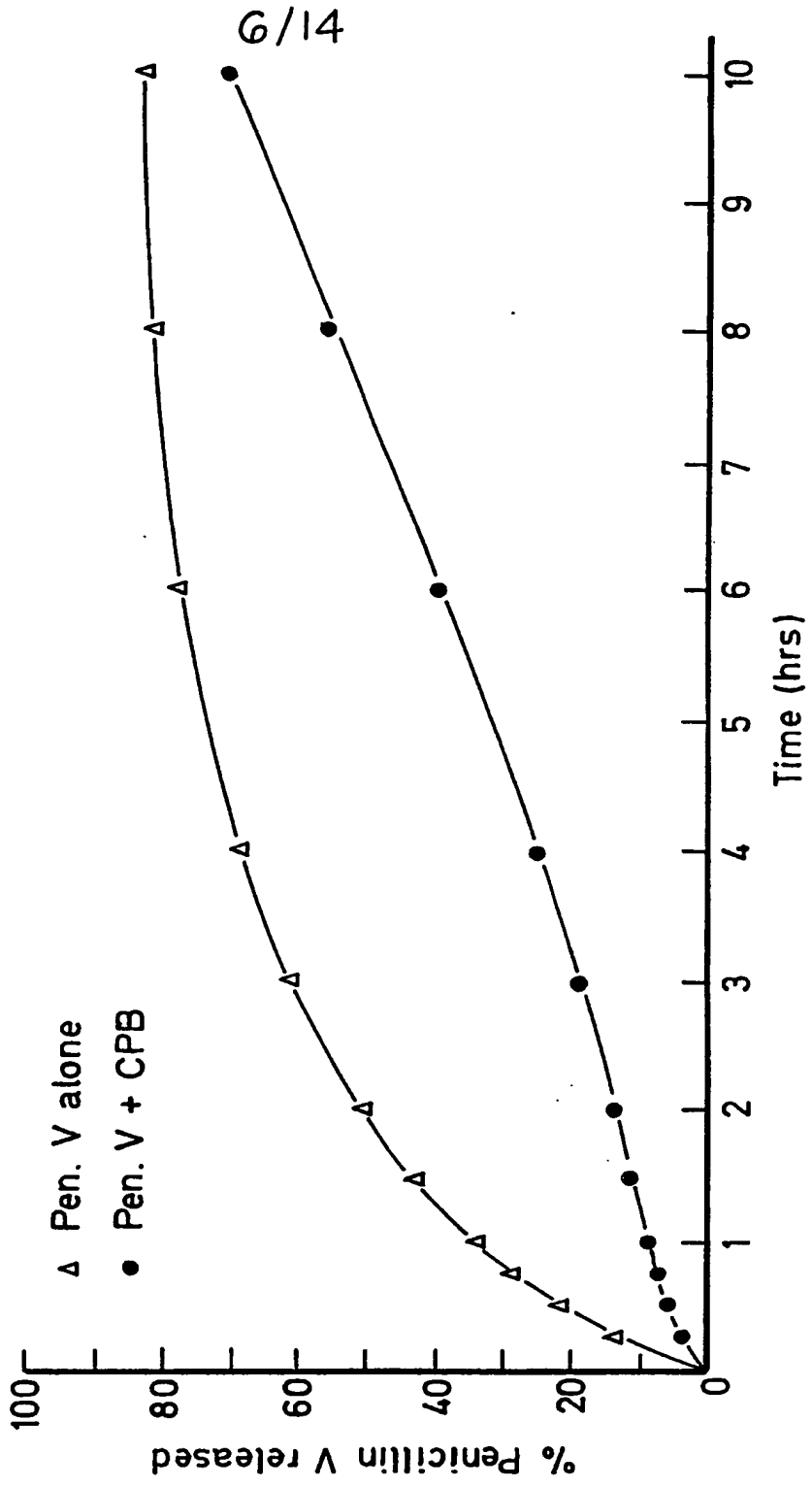


Fig.6. Effect of cetylpyridinium bromide (CPB) on Penicillin V release

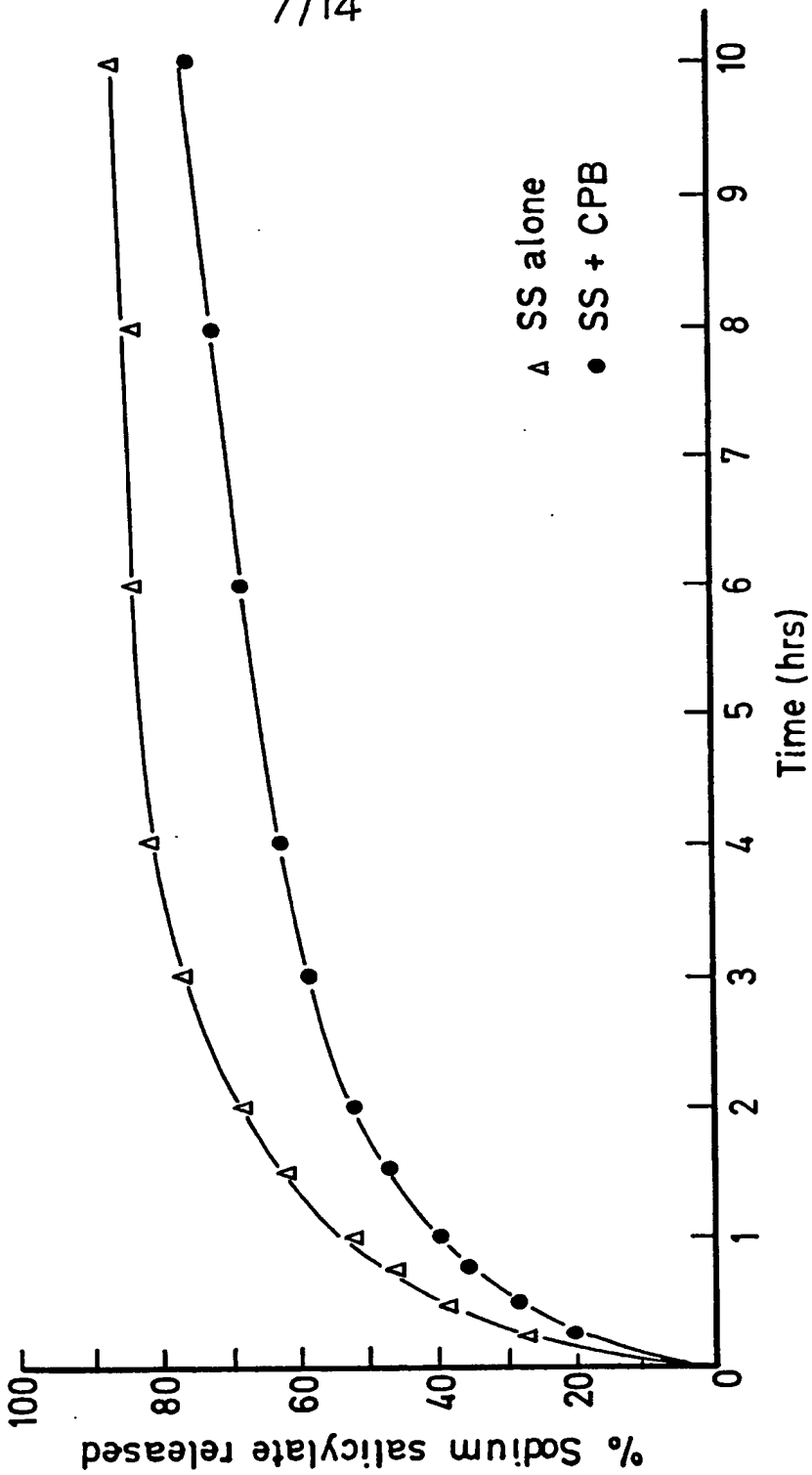


Fig. 7. Effect of cetylpyridinium bromide on release of sodium salicylate (SS)

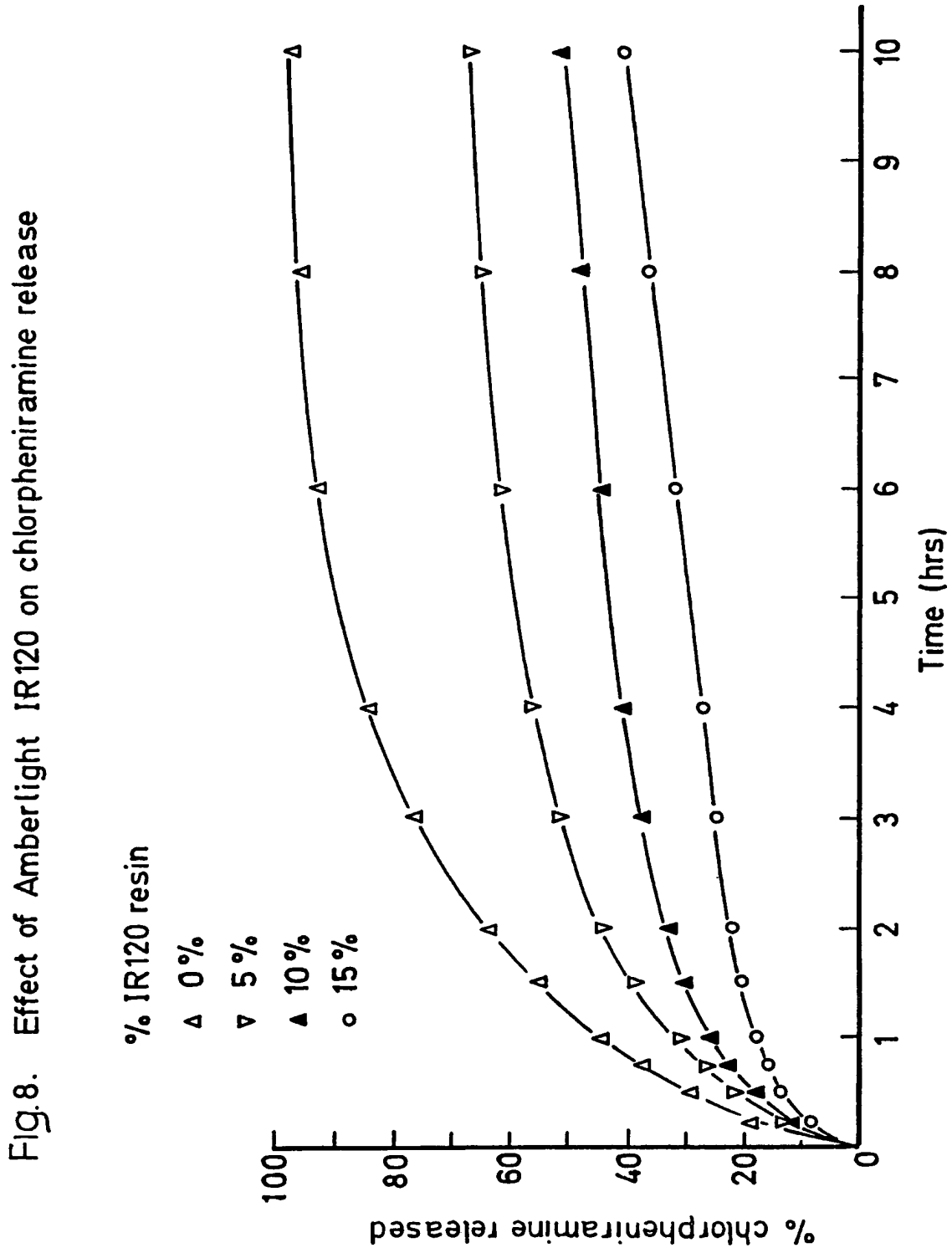


Fig.8. Effect of Amberlight IR120 on chlorpheniramine release

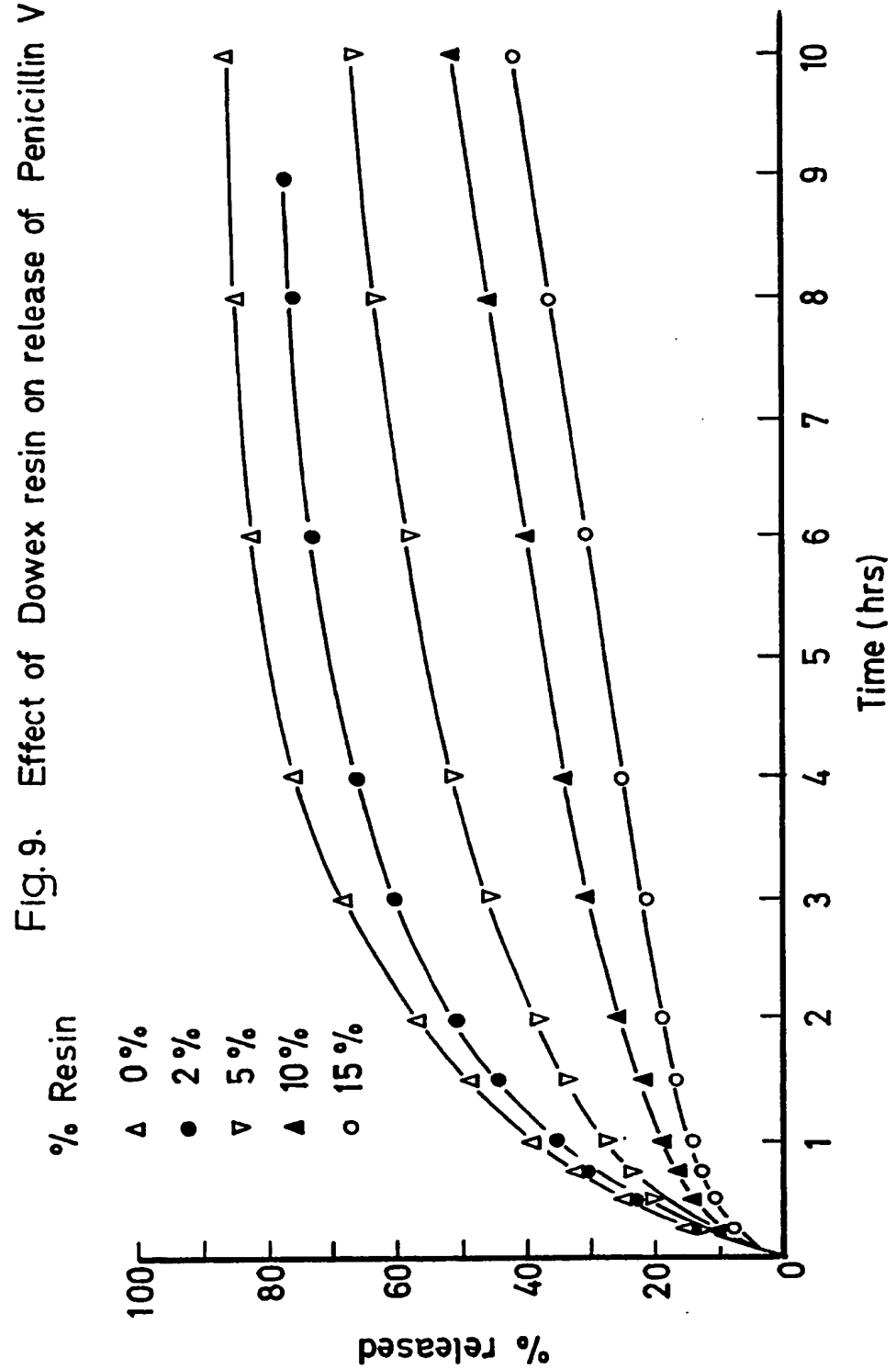


Fig. 9. Effect of Dowex resin on release of Penicillin V

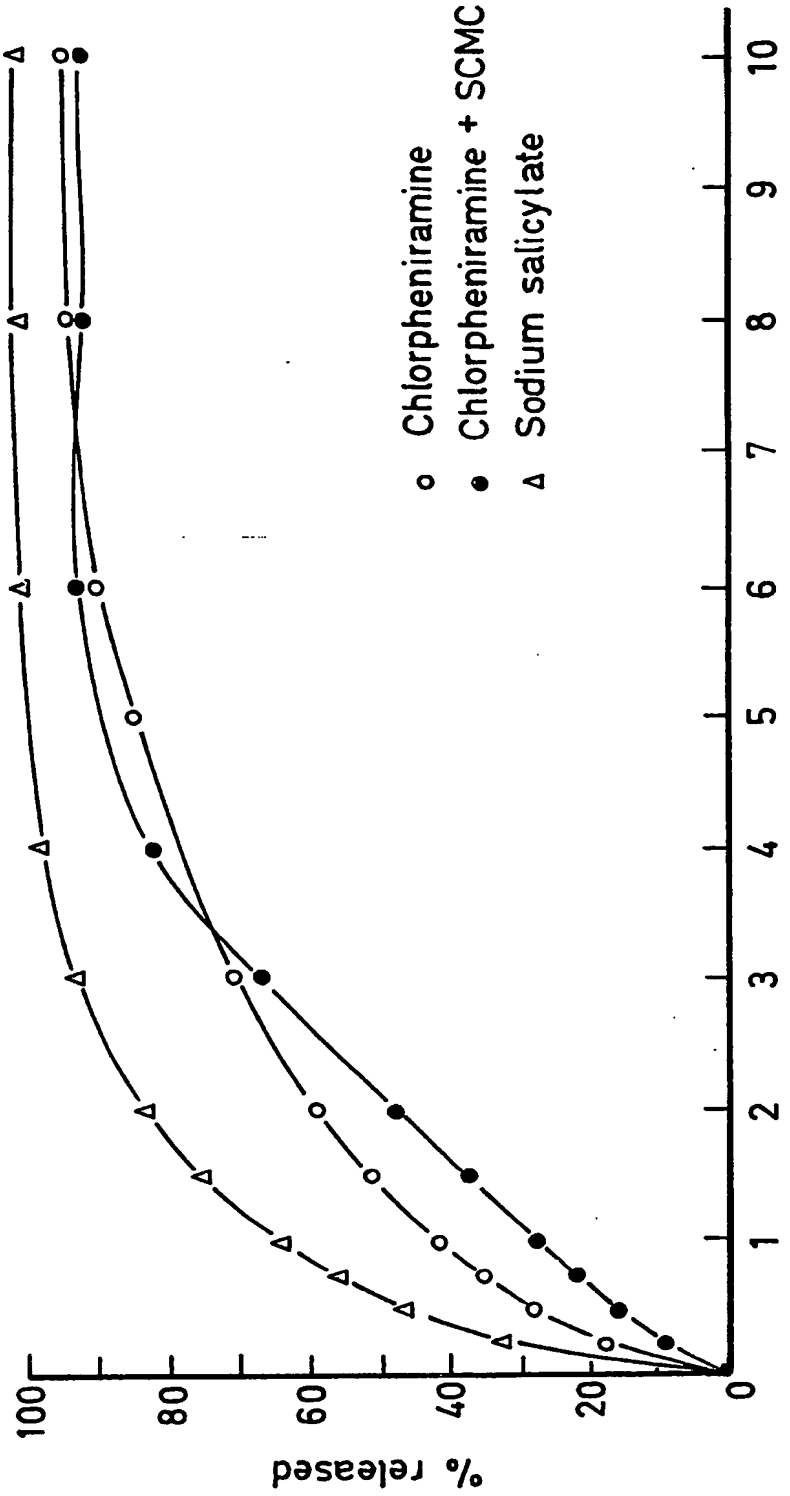


Fig. 10. Effect of ionic polymers on release from K100M tablets.

Fig. 11. Plot of [SOS] *v* 1/[Chl] for complexation

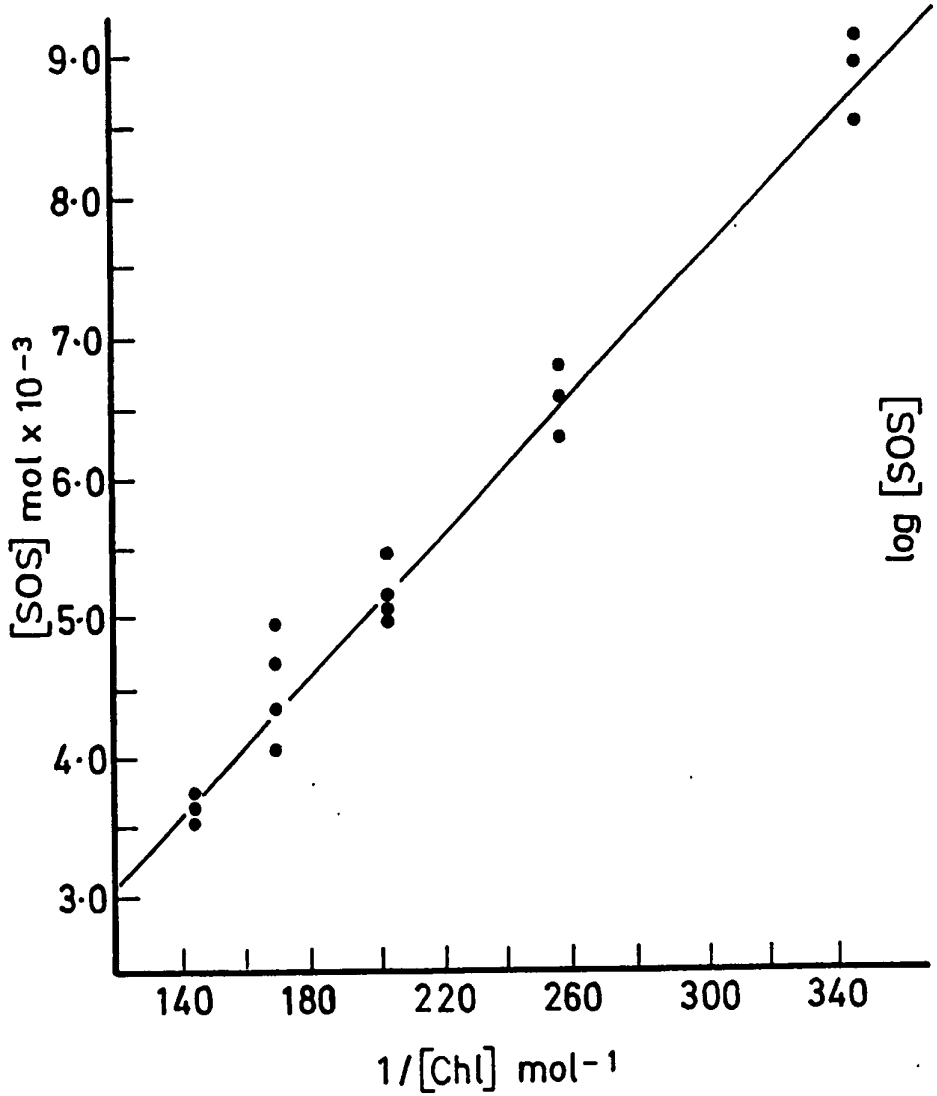
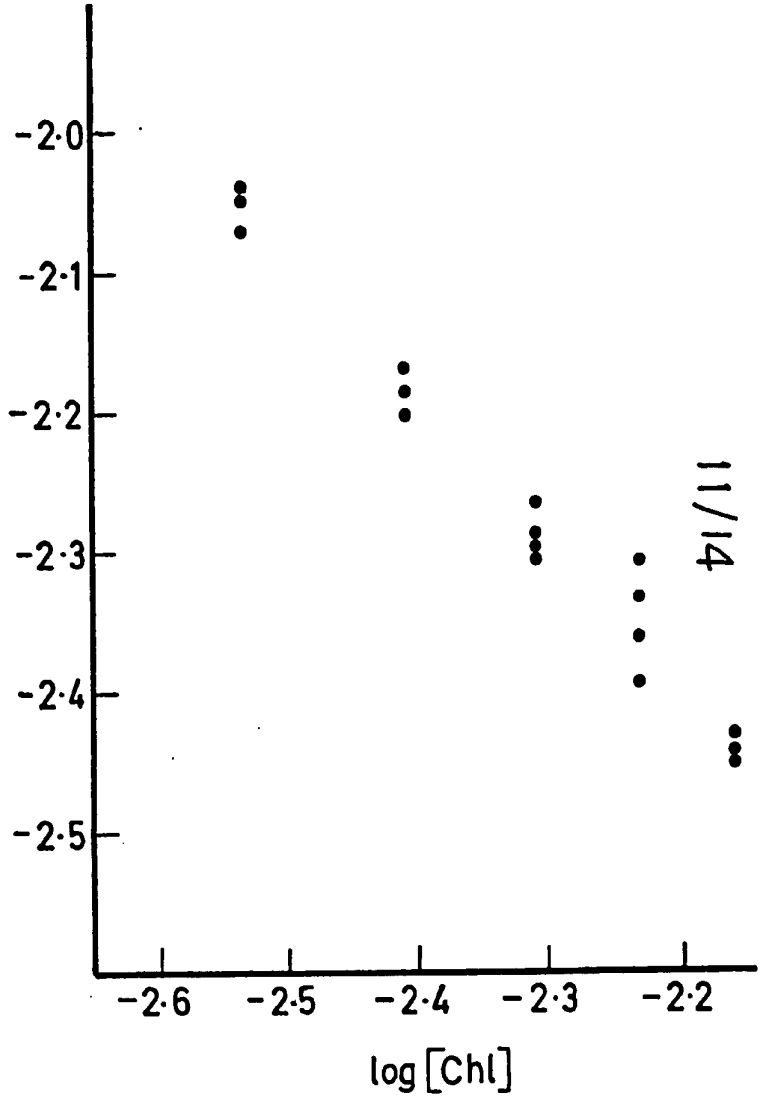


Fig. 12. Plot of log [SOS] *v* log [Chl]



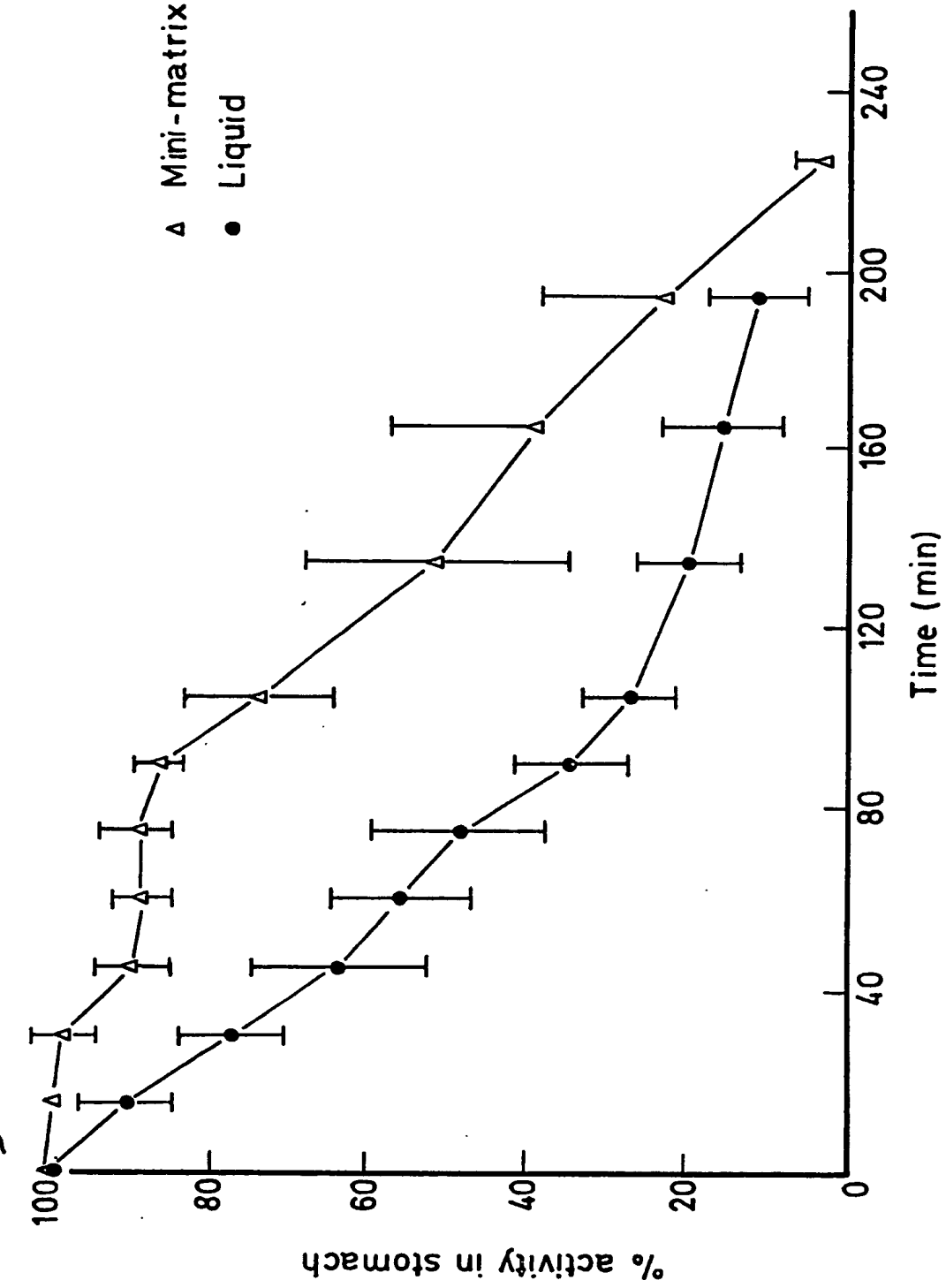
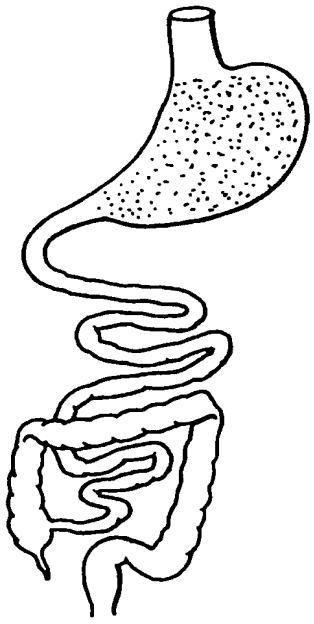
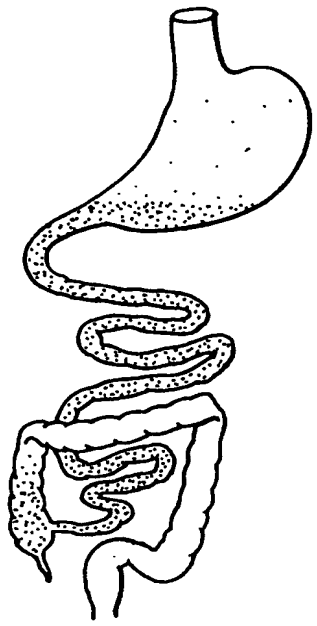


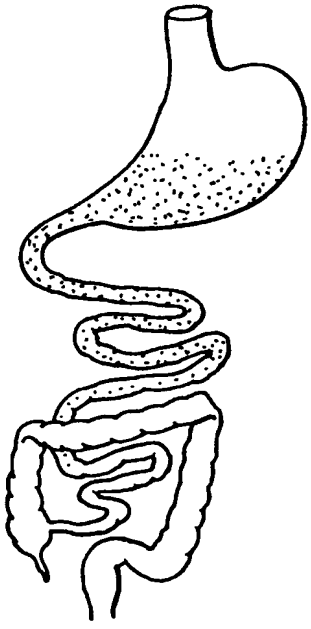
Fig.13 Gastric emptying of liquid and mini-matrices in fed volunteers.



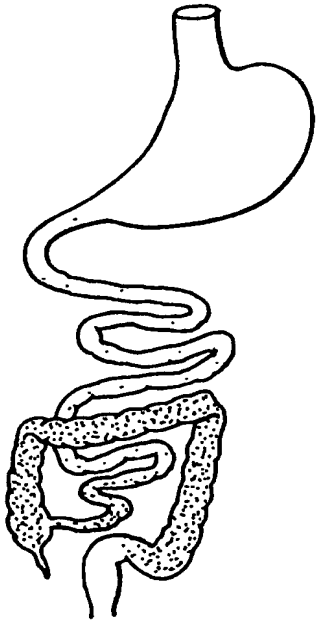
TIME 0.25h – Stomach 100%



TIME 2·25h – Stomach 10%



TIME 1·75h – Stomach 49%



TIME 7·75h – Stomach 0%

Fig. 14 Gastrointestinal transit of mini-matrices in a fed volunteer

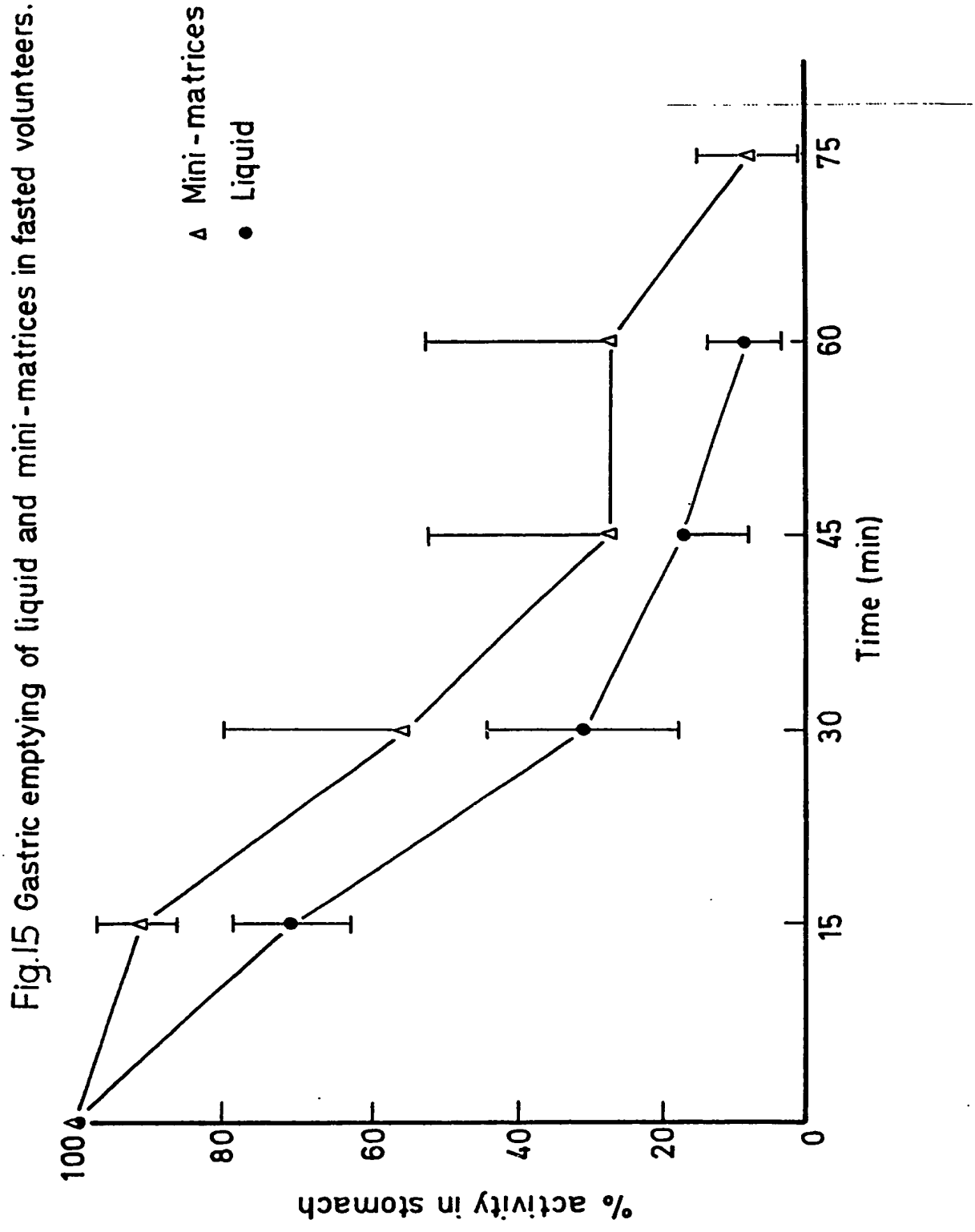


Fig.15 Gastric emptying of liquid and mini-matrices in fasted volunteers.

SPECIFICATION

Sustained Release Medicament

The present invention relates to sustained release medicaments and more particularly to a multi-particulate delivery system designed for administration to a bio-system.

A first known sustained release system comprises a single large tablet which is made by pressing a mixture of the active medicament a carrier and possibly other inactive fillers see for example U.S. 4,389,393. When in use in a biosystem the carrier which may be for example HPMC (hydroxypropyl-methylcellulose) is active to release the active medicament in a controlled manner by swelling and only allowing the active medicament to diffuse slowly. An advantage with such large tablets is that they are relatively cheap to make since they are made by a single pressing action. A disadvantage is that they are a single relatively large unit and they release the active medicament from a single entity. If therefore the tablet becomes lodged in a particular area of the biosystem the active ingredient is all released locally and this will result in poor administration of the medicament and may cause damage if the medicament is irritant.

To overcome the above disadvantages the multi-particulate type of medicament filled into a capsule has now become popular to achieve the sustained release action. In this type the active medicament is contained within a larger number, normally one hundred or more, tiny spheres normally less than 2 mm diameter which are contained within a quick dissolving capsule. When taken orally the capsule dissolves and the spheres are released and spread through the biosystem thereby avoiding any problem of too high a localised concentration of the active ingredient and also avoiding the problem of the large tablet becoming lodged in a particular spot in the biosystem.

The disadvantage with this known capsule multiparticulate system is in the cost of producing the tiny spheres. Each sphere has to be produced individually. For example, by a process involving producing a smaller inner sphere which contains the active medicament usually in a fairly concentrated form. Each inner sphere is then subjected to a series of coating processes which surround the inner sphere with a coating which allows only slow diffusion of the active medicament through the coating and hence gives the sustained release action.

It is an object of the present invention to provide a sustained release medicament which is substantially cheaper to produce than the previously known multiparticulate capsule type and which does not suffer from the disadvantages of the single tablet form.

According to the present invention there is provided a sustained release medicament comprising a multiparticulate delivery system designed for administration to a biosystem, the particles of which system including

Component A) an ionically charged bioactive ingredient or salt or ester of same,

Component B) a release-sustaining and binding medium selected from natural and synthetic polymers having anhyroglucose-based units in their backbone; and

Component C) an ionic substance having a charge opposite that of component A, or a salt or ester of said substance,

wherein the ratio of Components A, B and C is selected so as to reduce the rate of release of Component A to the biosystem from the particles of the delivery system when compared to the rate of release of Component A from a single tablet comprising the same amounts of Components A and B without Components C.

The invention also provides in a preferred embodiment a delivery system which is contained in a gelatin or other rapidly dissolving capsule.

In a further preferred form in the delivery system Component A is selected for administration due to its bioactivity in warm blooded animals.

Preferably in the delivery system Component C is selected from the group of polymeric materials of sufficiently high molecular weight or insolubility as to be inert with respect to the biosystem to which it is designed to be administered.

In a preferred system Component C is preferably selected from finely comminuted particles of cross-linked ion exchange resins.

In a further preferred system Component B is selected from alkyl cellulose ethers.

In a further preferred system Component B is selected from hydroxyalkyl alkylcellulose ethers and in an alternative preferred system Component B is selected from methylcellulose ethers.

Component B may preferably be selected from hydroxypropylmethylcellulose ethers.

The present invention also provides a process for making a multiparticulate delivery system mixing A, B & C to form a substantially homogeneous mixture,

forming a plurality of individual small tablets by a process of compression,

placing a plurality of said small tablets in a suitable container for oral application.

Embodiments of the present invention will now be described with reference to the accompanying drawings in which:—

Figure 1 shows a time release graph for a first embodiment of the present invention for a cationic drug (weak base);

Figure 2 shows a graph showing the effect of the concentration of alkyl sulphate on the release rate of the cationic drug (weak base) of Figure 1;

Figure 3 shows a time release graph showing the effect of a change in polymer on the release rate of a cationic drug (weak base) in a system according to the present invention;

Figure 4 shows a time release graph showing the effect of sodium carboxylate on the release of the cationic drug (weak base) in a system according to the present invention;

Figure 5 shows the effect of cationic surfactant on

the release of an anionic drug (weak base) in a system according to the present invention;

Figure 6 shows in particular the effect of cetylpyridinium bromide on the release of penicillin V;

Figure 7 shows in particular the effect of cetylpyridinium bromide on the release of sodium salicilate;

Figure 8 shows in particular the effect of Amberlite IR120 on the release of chloropheniramine;

Figure 8 shows in particular the effect of Dowex 2-X8 on the release of penicillin V;

Figure 10 shows the effect of ionic polymers on the release from K100M tablets;

Figure 11 shows a graph of concentration of sodium octyl sulphate (SOS) against the inverse of chloropheniramine maleate (CHI) to demonstrate ionic interaction between (SOS) and (CHI);

Figure 12 shows a graph of the log of the concentration of SOS against the log of CHI to demonstrate ionic interaction between (SOS) and (CHI);

Figure 13 shows gastric emptying of liquid and mini-matrices according to the present invention in fed volunteers;

Figure 14 shows the gamma scintagraphy record of the progress of mini matrices according to the present invention emptying from the stomach of a fed volunteer; and;

Figure 15 shows the graph of Figure 13 but for a fasted volunteer.

The present invention concerns the preparation of controlled release mini-tablets which are prepared by compressing directly a mixture of HPMC drug and excipient in order to produce a dosage form whose release profile is similar to that of a single, large, non-disintegrating sustained release table. The mini-tablets have been shown to give a more reproducible gastric emptying profile in vivo than a large non-disintegrating tablet. This provides more consistent bioavailability profiles. The mini-matric tablets are preferably contained in a quick dissolving capsule for administration. The capsule may preferably contain between ten and twenty mini-tablets but more or less could be used.

In a first embodiment of the present invention the release of a cationic drug (to include a wide variety of drug substances that are weak bases) from HPMC matrices is retarded by the use of an anionic surface active agent in the form of sodium lauryl sulphate. Retardation increases with increasing the amount of surfactant added. Other similar surfactants would be expected to have a similar retarding effect. This retardation effect is used to provide similar release profiles for the drug when administered as the mini-matrix as would be obtained from the conventional single unit matrix system. In the first embodiment the formular for the mini-tablet mix is as follows:

Methocel K100M HPMC		70%
chloropheniramine maleate		15%
sodium lauryl sulphate		x%
lactose B.P.	to	100%

in which x has values of 5, 10, 15, %. The retardation effects can be seen in Figure 1.

The tablet diameter was approximately 5 mm, tablet weight about 50 mg, compaction pressure about 170 MNm^{-2}, particle size of powders 127—180 micron size fraction. USP rotating paddle method was used, 5 cells. 900 ml of phosphate buffer at pH 7.0, 37 degrees, 4 tablets per cell, analysis by u.v. absorbance at 264.5 nm. A tablet size of 2 mm may be used with sixteen tablets per capsule. If percentage released is plotted against root time (for 0—240 mins) a straight line is obtained with a gradient K. A plot of K against molar surfactant added produces a straight line.

The retarding abilities of the alkyl sulphate surfactants on the release of chloropheniramine from HPMC matrices is dependent on the number of moles of surfactant present and independent of the chain length of the surfactant. Repeating the above experiments for other alkyl sulphates (sodium hexyl sulphate, sodium octadecyl sulphate) and plotting the K value against moles of alkyl sulphate per tablet produces a straight line as shown in Figure 2. There is no significant difference between the lines for the homologues used.

The retarding ability of sodium lauryl sulphate on chloropheniramine release is greater than K100M is used (Figure 3). Therefore it appears that the viscosity of the HPMC is important when surfactants are used to retard drug release. The release of chloropheniramine has been retarded by the use of an anionic carboxylate surfactant (sodium laurate). The retarding effect is dependent upon the amount of carboxylate added (Figure 4). The method of making the mini-tablets and dissolution testing was as above except that the surfactant was different. Sodium laurate did not have as great an effect as sodium lauryl sulphate indicating that the head group of the surfactant is important in retarding release.

In a second embodiment of the present invention the release of an anionic drug (to include many drugs that are weak acids) such as sodium salicylate BP is retarded by the use of a cationic surface active agent such as hexadecyltrimethylammonium bromide (HDTMAB). Mini-tablets were made according to the following formula:

Methocel K100M	70%
Sodium salicylate	15%
HDTMAB	15%

The physical characteristics of thz tablets and their production was as with reference to Figure 1 except that 296.0 nm was used as the analysis wavelength (Figure 5).

The release of sodium salicylate and penicillin V B.P. is retarded using the cationic surfactant cetylpyridinium bromide. The formula for the mini-tablet was as follows:

Methocel K100M	70%
Sodium salicylate or Penicillin V	15%
Cetylpyridinium bromide	15%

The analysis wavelength for penicillin V was 275.5 nm (Figures 6 and 7).

The release of chloropheniramine from HPMC mini-matrices retarded by the use of the cationic exchange resin Amberlite IR 120. Release rates are highly dependent upon the quantity of resin incorporated. A preferred formula used was:

Methocel K100M		70%
Chloropheniramine maleate		15%
Amberlite IR 120		x%
lactose B.P.	to	100%

The quantity for resin used was 2, 5, 10 and 15% (Figure 8).

The release of Penicillin V from K100M matrices has been retarded by the use of Dowex 2-XB anionic exchange resin. Release rates are highly dependent upon the amount of resin used. A preferred formula used was:

Methocel K100M		70%
Penicillin V B.P.		15%
lactose B.P.	to	100%

The quantity of resin used was 2, 5, 10, and 15% (Figure 9).

The release profile of chloropheniramine from K100M matrices has been altered by the presence of sodium carboxymethyl cellulose. A preferred formula used for the mini-tablet was:

Methocel K100M	42.5%
chloropheniramine maleate	15%
sodium CMC	42.5%

release curves are shown in Figure 10.

Other polymeric materials having positive and negative charged groups should also be effective in retarding the release of drugs that are weak acids and weak bases. Materials employed in the food industry should be suitable, for example xanthan gum.

In all the above cases the charge interaction of the drug with the excipient appears to be the major factor in reducing the release rate of the drug. Sodium octyl sulphate has been found to complex with chloropheniramine maleate to form a 1:1 complex with a solubility product of 2.58×10^{-5} mol $2\,l^{-2}$ (Figures 11 and 12). Such a complex is less likely to release from the matrix quickly because of its lower solubility.

In a practical test a dosage form containing 16 controlled release HPMC mini-matrices within a hard gelatin capsule were administered to each of 4 human volunteers and their gastrointestinal transit followed using the technique of gamma scintigraphy. When taken after a light breakfast (cornflakes with milk, two slices of toast with butter and a cup of tea) the tablets emptied gradually after an initial lag period. The tablets appeared to spread within the small intestine and as such behaved more as a pellet system than a large non-disintegrating tablet (Figure 13 and Figure 14). The more predictable gastrointestinal transit and the spreading of the tablets in the small intestine should lead to a more predictable drug absorption profile than would be expected from a conventional single unit matrix system.

The tablet diameter was 3.1 mm and the tablet weight 16 mg. The number of tablets per capsule was sixteen in a capsule size 0.

In more detail radiolabelled mini-matrices were prepared by blending 15% w/w of Indium-111 labelled Amberlite IR 120 resin (BDH Chemicals) with 85% w/w of Methocel K100M grade HPMC (Colorcon) and then directly compressing the mix on a Manestry F3 single punch tablet machine. The tablets had a mean diameter of 3.1 mm and a mean weight of 16 mg.

The *in vitro* dissolution rate of the Indium-111 labelled resin was measured using the USP rotating basket method at 100 rpm. A phosphate buffer (pH 7.0) of constant and low ionic strength was used as the dissolution medium. At each sampling interval the tablets were removed carefully from their baskets and assayed using a Spectro Type 5350 radioactivity counter (ESI Nuclear).

The practical test involved four healthy, non-smoking, male volunteers (age 19—24, weight 60 kg—95 kg, height 1.70 m—1.78 m) who were not taking medication, had abstained from alcohol for 24 hours and had fasted overnight. Two of the volunteers were given a light breakfast (cereals with milk, two slices of toast with butter and a cup of tea) immediately before the study; the other two volunteers remained fasted. Each subject ingested sixteen Indium-111 labelled mini-matrices (either individually or contained with a hard gelatin capsule) and also 200 ml of a Technetium—99 m diethylenetriaminepenta-acetic acid labelled drink.

An external anatomical marker radiolabelled with Technetium—99 m was taped on each subject, anteriorly over the right lobe of the liver. Imaging was undertaken with the subjects standing, using a General Electric Maxicamera Type II having a 40 cm diameter field of view, fitted with a medium energy parallel hole collimator and linked to a Nodecrest computer. For each image obtained a region of interest was drawn around the position of the stomach and the activity count in this region was noted. The count was corrected for background, scatter down (the scatter of the Indium—111 into the energy window of the Technetium—99 m) and then radioactive decay. The geometric mean of anterior and posterior counts was used to give a result independent of the depth of the source. The corrected counts were plotted as a percentage of the initial count against time.

A crossover study was carried out seven days later such that those subjects given breakfast originally were fasted and vice versa.

The *in vitro* dissolution of the radiolabelled tablets showed that 63% of the Indium—111 was still within the tablets after five hours. It therefore appears reasonable to assume that the Indium—111 images relate to the position of the mini-matrices *in vivo*.

The gastric emptying profiles for subjects given breakfast are shown (Figure 13). The Technetium—99 m labelled liquid emptied exponentially with a

mean T50% (time for 50% to empty from the stomach) of 70 minutes (SD 20 minutes). The mini-matrices emptied linearly after an initial lag phase of 90 minutes and with a T50% of 140 minutes (SD 35 minutes).

Figure 14 shows the mini-matrices emptying gradually from the stomach of a fed volunteer. The tablets appear to spread within the small intestine and then regroup once they enter the large intestine at about eight hours after ingestion.

In fasted volunteers (Figure 15) emptying occurred very quickly for both liquid and tablets. No lag phase was observed and the tablets emptied more as a bolus. Gastric emptying was virtually complete by 75 minutes. The interdigestive myoelectric complex ("housekeeper effect") may be the reason for this sudden bolus emptying of the tablets. When digestion is complete the motility pattern of the intestine changes from a fed mode to a fasting mode. During the fasting mode large, sweeping, peristaltic waves remove all undigested material from the stomach down through the small intestine. This type of motility pattern should be present in all of the fasted subjects provided that the dosage forms were not sufficient to promote a digestive pattern.

Small intestinal transit times were also calculated by subtracting the time for 90% of the tablets to empty from the stomach from the time for 90% to reach the ascending colon. There was no significant difference in transit times between fed subjects (mean 220 minutes, SD 75 minutes) and fasted subjects (mean 300 minutes, SD 70 minutes).

It may be concluded therefore that the transit of a small number of mini-matrices through the GI tract is more predictable than that reported for single large, non-disintegrating tablets. When taken after food, the mini-matrices empty gradually, spread in the small intestine and regroup in the colon. Transit times through the small intestine are independent of the food content of the stomach.

CLAIMS

1. A sustained release medicament comprising a multiparticulate delivery system designed for administration to a biosystem, characterised in that the particles of the system include

Component A) an ionically charged bioactive ingredient or salt or ester of same,

Component B) a release-sustaining and binding medium selected from natural and synthetic polymers having anhydrogluclose-based units in their backbone; and

Component C) an ionic substance having a charge opposite that of component A, or a salt or ester of said substance,

wherein the ratio of Components A, B and C is selected so as to reduce the rate of release of Component A to the biosystem from the particles of the delivery system when compared to the rate of release of Component A from a single tablet comprising the same amounts of Components A and B without Components C.

2. A sustained release medicament as claimed in Claim 1 characterised in that Component A is selected for administration due to its bioactivity in warm blooded animals.

3. A sustained release medicament as claimed in Claim 1 or Claim 2 characterised in that Component C is selected from the group of polymeric materials of sufficiently high molecular weight or insolubility as to be inert with respect to the biosystem to which it is designed to be administered.

4. A sustained release medicament as claimed in any one of Claims 1 to 3 characterised in that Component C is preferably selected from finely comminuted particles of cross-linked ion exchange resins.

5. A sustained release medicament as claimed in any one of Claims 1 to 4 characterised in that Component B is selected from alkyl cellulose ethers.

6. A sustained release medicament as claimed in any one of Claims 1 to 4 characterised in that Component B is selected from hydroxyalkyl alkylcellulose ethers or from methylcellulose ethers.

7. A sustained release medicament as claimed in any one of Claims 1 to 4 characterised in that Component B is selected from hydroxypropyl-methylcellulose ethers.

8. A sustained release medicament as claimed in any one of Claims 1 to 7 characterised in that the delivery system is contained in a gelatin or other rapidly dissolving capsule.

9. A process for making a sustained release medicament including a multiparticulate delivery system characterised by mixing Components A, B & C as hereinbefore claimed to form a substantially homogeneous mixture,

forming a plurality of individual small tablets by a process of compression,

placing a plurality of said small tablets in a suitable container for oral application.

10. A sustained release medicament substantially as described with reference to the accompanying drawings.

11. A process for making a sustained release medicament substantially as described with reference to the accompanying drawings.

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